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Green multicomponent efficient approach to (aryl)di(hetaryl)methanes bearing barbituric and hydroxypyridone moieties

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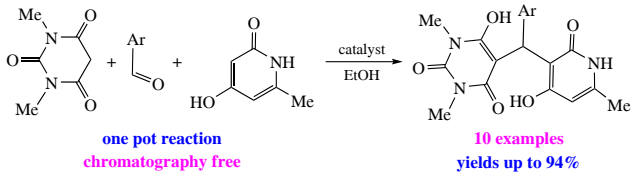
The new multicomponent Knoevenagel–Michael reaction between benzaldehydes and two different CH-acids, *N*,*N*′-dimethylbarbituric acid and 4-hydroxy-6-methylpyridin-2(1*H*)-one, proceeds in refluxing ethanol in the presence of TsOH and affords the (aryl)di(hetaryl)methane products, namely, 5-[(aryl)(2-oxo-1,2-dihydropyridin-3-yl)methyl]-pyrimidine-2,4(1*H*,3*H*)-diones, in 73–94% yields. The products contain two N-heterocyclic pharmacophore moieties and seem promising for biomedical applications.



Keywords: multicomponent reaction, tandem Knoevenagel–Michael reaction, benzaldehydes, barbituric acids, 4-hydroxy-6-methylpyridin-2(1*H*)-one, [(aryl)(dihydropyridin-3-yl)methyl]pyrimidines.

Green chemistry is focused on the design of processes and products to minimize or to eliminate the use and generation of hazardous substances.[1] Carbon–carbon bond formations are the general processes in organic synthesis for the construction of the complex frameworks or scaffolds from simple and usual organic molecules.[2] The development of the new synthetic strategies for the C–C bonds formation is one of the main ideas for both academic and industrial researchers in organic chemistry.[3] Multicomponent reactions (MCRs) are now synthetic routes in a diversity-oriented way to maximum structural complexity in minimum steps.[4] They employ multiple starting compounds which react in a stepwise manner to yield complex products in a greener and more economical manner.[5,6] Unlike traditional methods, MCRs increase the accessible chemical space exponentially with each additional reaction component.[7,8]

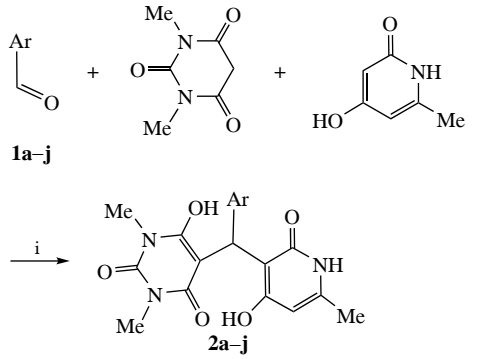
Tandem reactions are the processes with several reaction stages, which follow one after another, and the sequent stage is dependent on the type of new functional groups formed in the previous one.[9] Tandem Knoevenagel–Michael reaction is also known in organic chemistry,[8] and until now, investigations in this area have been in progress.[10–13]

Heterocyclic compounds play a significant role in drug discovery due to their unique structural and electronic properties, which allow them to interact with different receptors and enzymes.[14] Thus, a great number of heterocyclic compounds and fragments are present in many drugs.[15]

The use of privileged structures or scaffolds is a widely developing area in pharmacology. The usage of these definitions could allow the medicinal chemist more rapidly discover biologically active molecules with a broad range of therapeutic activities.[16] The barbiturate (pyrimidine-2,4,6-trione) scaffold is an important building block for the development of pharmacologically active compounds, synthetically useful frameworks, supramolecular host–guest architectures, and functionalized materials.[17] In medicinal chemistry, barbiturates are used as a privileged medicinal structure, as they bear a broad range of therapeutic properties.[18,19] A renewed interest in this class of compounds arose as the pyrimidinetrione template was found to be the efficient zinc-chelating moiety and have high selectivity toward matrix metalloproteinases, which are responsible for cancer progression.[20] Also, barbiturates demonstrated inhibition against protein kinase C,[21] which is a target for therapeutic intervention in immunological disorders, human immuno-deficiency virus, and rheumatoid arthritis, as well as inflammatory diseases.[22]

Among other N-containing heterocycles, 4-hydroxy-6-methylpyridin-2(1*H*)-one is an important block that could serve as a hydrogen bond donor and acceptor.[23] Pyridinone derivatives exhibit various biological activities ranging from antitumor, antimicrobial, anti-inflammatory, and anti-coagulant to cardiotonic effects.[24] 2-Pyridinone derivatives have been found to be the potent and selective non-nucleoside inhibitors of HIV-1 reverse transcriptase.[25] The 4-hydroxy-6-methylpyridin-2(1*H*)-one scaffold is also a part of the natural pyrimidine nucleoside that is involved in RNA and bio-membrane synthesis,[26] galactose metabolism,[27] modulation of reproduction,[28] and peripheral[29] and central nervous systems activities.[30] Thus, combinations of pharmacologically active pyrimidine-2,4,6-trione scaffold with a bioactive 4-hydroxy-6-methylpyridin-2(1*H*)-one fragment should force and multiplicate properties of the both privileged scaffolds.

Considering our experience in multicomponent reactions with the formation of complex heterocyclic compounds and biomedical applications of N-heterocyclic scaffolds, we intended to design a convenient and efficient tandem Knoevenagel–Michael strategy assembling aromatic aldehydes **1a–j**, *N*,*N*′-dimethylbarbituric acid, and 4-hydroxy-6-methylpyridin-2(1*H*)-one into non-symmetrical 5-[(aryl)(1,2-dihydropyridin-3-yl)methyl]pyrimidine-2,4(1*H*,3*H*)-diones **2a–j** with two pharmacologically active N-heterocyclic rings (Scheme 1).



a Ar = Ph (91%)
b Ar = 3-MeC_6H_4 (82%)
c Ar = 4-EtC_6H_4 (75%)
d Ar = 3-MeOC_6H_4 (73%)
e Ar = 2,3-(MeO)$_2C_6H_3$ (78%)
f Ar = 2,5-(MeO)$_2C_6H_3$ (89%)
g Ar = 4-ClC_6H_4 (87%)
h Ar = 3-BrC_6H_4 (94%)
i Ar = 2,3-$Cl_2C_6H_3$ (78%)
j Ar = 4-$O_2NC_6H_4$ (75%)

Scheme 1 *Reagents and conditions*: i, catalyst, EtOH, reflux, 4 h.

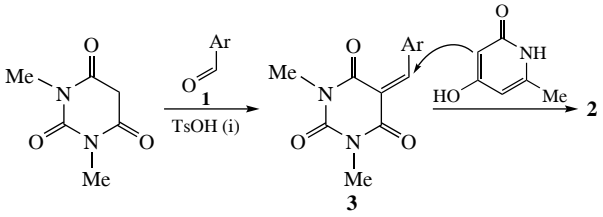
Initially, to optimize the reaction conditions with model benzaldehyde **1a**, we have carried out the multicomponent synthesis of 5-[(1,2-dihydropyridin-3-yl)(phenyl)methyl]-pyrimidine-2,4(1*H*,3*H*)-dione **2a** under solvent-free[31,32] conditions (Table 1, entries 1,2). Under these conditions, the result was unsatisfactory. Under the 'on-water' conditions[33,34] (entries 3,4) the yield of compound **2a** did not exceed 15%. Then, this transformation was studied in alcohol media (entries 5–16). The reaction in refluxing ethanol without a catalyst for 2 h provided a 28% yield of **2a** (entry 5); meanwhile, the addition of a base catalyst increased the yield up to 45% (entries 6–10). Iodine,[35,36] TsOH,[37,38] and sulfamic acid[39] were previously documented as the catalysts for the tandem Knoevenagel–Michael reactions. In this work, with iodine and TsOH product **2a** was obtained in 53 and 59% yields with 2 h reaction time (entries 11,12).

Finally, the best conditions found involved the use of TsOH as the catalyst and 4 h heating: under these conditions product **2a** was obtained in 92% yield (see Table 1, entry 13). Under the optimal conditions, other compounds **2b–j** were formed in 73–92% yields (see Scheme 1). In all these multicomponent processes, after the end of the reaction, the reaction mixture was

Table 1 Optimization of the reaction conditions between benzaldehyde **1a**, *N*,*N*′-dimethylbarbituric acid, and 4-hydroxy-6-methylpyridin-2(1*H*)-one toward compound **2a**.[a]

Entry	Solvent	Catalyst	Quantity of catalyst (mol%)	*T*/°C	*t*/h	Yield of **2a** (%)
1	–	–	–	22	5	8
2	–	NaOAc	10	22	5	12
3	H_2O	–	–	80	2	5
4	H_2O	NaOAc	10	80	2	15
5	EtOH	–	–	78	2	28
6	EtOH	NaOAc	10	78	2	42
7	EtOH	NaOH	10	78	2	34
8	EtOH	morpholine	10	78	2	34
9	MeOH	NaOAc	10	65	2	40
10	Pr^{i}OH	NaOAc	10	96	2	45
11	EtOH	I_2	10	78	2	53
12	EtOH	TsOH	10	78	2	59
13	EtOH	TsOH	10	78	4	92
14	EtOH	TsOH	10	78	6	88
15	Pr^{i}OH	TsOH	10	96	4	85
16	EtOH	TsOH	20	78	4	87

[a] Benzaldehyde **1a** (1 mmol), *N*,*N*′-dimethylbarbituric acid (1 mmol), 4-hydroxy-6-methylpyridin-2(1*H*)-one (1 mmol) with or without catalyst were refluxed in a solvent (4 ml) at indicated temperature.



Scheme 2 *Reagents and conditions*: i, TsOH (10 mol%), EtOH, reflux, 4 h.

filtered, the solid was rinsed with an ice-cold ethanol/water solution (1 : 1), and dried under reduced pressure. The structure of new compounds **2a–j** was confirmed by ^{1}H, ^{13}C NMR, and IR spectroscopy, as well as mass spectrometry data.

In view of the known data on the tandem Knoevenagel–Michael reactions of carbonyl compounds and CH acids,[40] the mechanism for the current transformation has been proposed (Scheme 2). In the first step, the condensation of benzaldehyde **1** and *N*,*N*′-dimethylbarbituric acid in the presence of TsOH results in the Knoevenagel adduct **3**. The following Michael addition of 4-hydroxy-6-methylpyridin-2(1*H*)-one to the electron-deficient olefin **3** leads to the final (aryl)di(hetaryl)-methane product **2a**.

In summary, the new type of catalytic one-pot Knoevenagel–Michael reaction was found: the direct multicomponent assembly of non-expensive aromatic aldehydes **1**, *N*,*N*′-dimethylbarbituric acid, and 4-hydroxy-6-methylpyridin-2(1*H*)-one into 5-[(aryl)-(1,2-dihydropyridin-3-yl)methyl]pyrimidine-2,4(1*H*,3*H*)-diones **2** in 73–94% yields. The compounds thus formed seem promising for different biomedical applications, among them anticonvulsants, anti-AIDS agents, and anti-inflammatory remedies. Mild and facile conditions of this multicomponent process make it valuable for the creation of new potential drug libraries.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7766.

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